Chartered Patent Attorneys
European Patent Attorneys
Trade Mark Attorneys
European Trade Mark Attorneys

Telephone +44 (0)20 7242 0901
Fax +44 (0)20 7242 3290/0286
E-mail r&g@reddie.co.uk
Website www.reddie.co.uk

Reddie & Grose

16 Theobalds Road
London WC1X 8PL

Richard C. Abnett M.A.
Paul A. Brereton M.A.
Nicholas S. Marlow B.Sc.
Linda J. Harland B.Sc.
Jonathan M. Davies D.Phil.
Patrick A.D. Lloyd B.Sc.
Aidan J. Robson M.Sc.
Helen R. Wakerley M.A.
Jan M. Vleck M.A.
Simon J.N. Goodman Ph.D.
Ian M. Loveless M.A.

Assisted by
David S. Jackson B.Sc.
Julie K. Richardson Ph.D.
Philip I. Bates Ph.D.

Consultants
Keith E. Geering B.A.
John H. Bass B.Sc.
F.A.B. Valentine M.A.

VAT No. GB 243 9087 49

CONFIRMATION

European Patent Office
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12 February 2002
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Dear Sirs,

EPO - Munich
3
15. Feb. 2002

European Patent Application No. 99906992.5
EPO Publication No: 1063987
WAKE FOREST UNIVERSITY
Our file: G3312

With regard to the patentability of the claims of the above application, attention is drawn under Article 115 EPC to the following documents. Two copies of each cited prior publication is enclosed with confirmation of this facsimile.

D1. Nassar *et al.*, Lipids 21, 652-656, 1986

D2. Nassar *et al.*, Nutrition Research Vol 6, 1397-1409, 1986

D3. Takashi *et al.*, Thrombosis Research 47, 135-146, 1987

D4. Horrobin and Manku, Omega-6 Essential Fatty Acids, Pathophysiology and Roles in Clinical Medicine, pages 21-53, 1990

D5. Huang and Nassar, Omega-6 Essential Fatty Acids, Pathophysiology and Roles in Clinical Medicine, pages 127-144, 1990

D6. Zurier *et al.*, Omega-6 Essential Fatty Acids, Pathophysiology and Roles in Clinical Medicine, pages 203-221, 1990

D7. PCT/GB97/02738 Pharmaceutical preparation comprising eicosapentaenoic acid and/or stearidonic acid.

D8. Flow Diagram

The composition claims of EP 99906992.5 are extremely broad, and relate to an open-ended composition comprising gamma linoleic acid (GLA) (or dihomogammalinoleic acid (DGLA)), a

delta-5-desaturase (D5D) inhibitor, and a competitive inhibitor of arachidonic acid (AA) metabolism such as eicosapentaenoic acid (EPA).

The mechanism of conversion of the n-6 and n-3 essential fatty acids was very well known at the time of filing the application. We attach a flow diagram, D8, summarising the conversion for the Examiner's convenience. This flow diagram is not prior art but the information disclosed therein has been described in many documents, see for example: D1, page 652; D2 page 1398; D3 page 141; D4 pages 22 and 26; D5 pages 129 and 134 to 136.

Looking at claim 3 and claim 5 to provide an example of a composition which falls within claim 1, we see a composition comprising: GLA (or DGLA), eicosapentaenoic acid (EPA) and stearidonic acid (SA). Of course other ingredients can be present.

GLA and DGLA are n-6 essential fatty acids. These are found in primrose oil and other oils like borage oil. EPA and SA are n-3 essential fatty acids. These are found in fish oil, for example polepa.

D1, D2, D3, D4, D5 and D6 disclose providing primrose oil and polepa as a dietary supplement. Each of these documents destroys the novelty of the claimed invention: there is disclosed a composition which includes all the features of claim 1.

The problem addressed by EP 99906992.5 is to provide a dietary supplement which increases levels of DGLA, without increasing the levels of arachidonic acid (AA). The solution proposed by the present application is to provide GLA or DGLA, together with an inhibitor of D5D and a competitive inhibitor of AA metabolism. The skilled man, having knowledge of the metabolism of these EFAs, as discussed in the art, would not require a step of inventive merit to provide a composition comprising amounts of GLA or DGLA, an inhibitor of D5D and a competitive inhibitor of AA, when seeking to increase the ratio of DGLA:AA and lessen the potentially harmful effects of AA/AA metabolites, and he knows the result will be beneficial. Indeed, this specific concept is explicitly proposed in the prior art, for example D1 to D5 and is experimentally illustrated by the effects of coadministration of GLA and EPA at a range of doses (D1 and D2).

AA is known to be intimately involved in human disease (description of EP 99906992.5 page 1, paragraph 2); AA is the precursor of TxA_2, PGF_2, and leukotrienes, which are "implicated in various disease entities ranging from thromboembolic phenomena to inflammation" (D1, column 2, paragraph2). TxA_2 is known to be a "potent proaggregatory and vasoconstrictor agent", and leukotrienes are known to be "strongly proinflammatory" (D4, page 24). Reduction of the levels of these metabolites of AA was clearly known to be desirable at the time of filing the application.

On the other hand, DGLA products, such as PGE_1 "either are neutral, or have a wide range of favourable actions" (D1, page 1, column 2, paragraph 2). PGE_1 is known to have a wide range of desirable effects, including "inhibiting platelet aggregation and inflammation, producing vasodilation, lowering blood pressure, raising cyclic AMP levels, and inhibiting phospholipases" (D4, page 23). Increasing the levels of these was clearly known to be desirable at the time of filing the application.

It is known that DGLA is converted to AA by D5D (see *inter alia* D1 to D6). It is quite clear,

therefore, that the person skilled in the art looking to increase the ratio of DGLA to AA would provide a composition comprising DGLA or GLA and an inhibitor of D5D.

In fact, use of inhibitors of D5D to increase levels of DGLA without increasing levels of arachidonic acid had already been described at the time of filing the application, see among others: D1, page 654 column 1; D2, page 1406 paragraph 2; D4, page 26; and D6 page 208, which notes suppression of inflamation by providing a combination of primrose seed oil and menhaden fish oil. This combination provides a composition comprising DGLA, and a D5D inhibitor.

The inhibitors of D5D of the art act to inhibit the D5D metabolism of DGLA, and at the same time the D5D metabolism of omega-3 arachidonic acid (omega-3 AA; also known as 20:4n-3). Thus, in use, levels of DGLA increase, as do those of omega-3 AA.

On page 11 of the specification, omega-3 AA is given as an example of a competitive inhibitor, competing with enzymes, eg phospholipase A2 (PLA2), which convert AA to oxygenated metabolites. To add into the starting composition a "competitive inhibitor" is obvious - this is aiming for the same result as the consequence of the D5D inhibitor action.

Fundamentally, the art recognises that SA and EPA have a role in AA metabolism. D7 notes that SA is as effective as EPA in the inhibition of PLA2 - EPA being a well known competitive inhibitor of the formation of AA from DGLA and of the conversion of AA to prostaglandins. It was thus well-known that SA and EPA would provide the competitive inhibitor of AA. Omega-3 AA would be expected to have the same effect. Thus a known composition of GLA (or DGLA) and EPA (see D1, D2, D3) has the effect of D5D inhibition and AA metabolism suppression and provides the elements of claim 1. SA rapidly elongates to omega-3 AA. There are no viable commercial sources of omega-3 AA; therefore, it is obvious to use SA.

As mentioned above, AA is known to be intimately involved in human disease, and DGLA products are widely known to have a range of desirable effects. The provision of a composition as described in EP 99906992.5 which alters the ratios of these compounds, and limits the action of AA is nothing more than what was known already.

Yours faithfully,

WAKERLEY, Helen Rachael
Professional Representative